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## **Mortality following congenital diaphragmatic hernia repair: the role of anaesthesia**

*Running head:* Anesthesia and congenital diaphragmatic hernia

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**What is already known**

- Infants with congenital diaphragmatic hernia (CDH) have a high post-operative mortality

**What this article adds**

- Neither the perioperative fluid volume nor the duration of anaesthesia were associated with increased post-operative mortality in infants with isolated CDH.
- The post-operative oxygenation index (OI) at 24 hours, but not the preoperative OI or best OI on day one predicted post-operative mortality.

## **Abstract**

*Background:* Mortality following surgical repair of congenital diaphragmatic hernia (CDH) remains high. The volume and type of peri-operative intravenous (i.v.) fluid administered, baro-trauma, oxygen toxicity and the duration of anesthesia are thought to affect outcome in surgical populations.

*Aims:* To determine whether the peri-operative volume or type of i.v. fluids and/or the duration of anaesthesia were associated with post-operative mortality and if mortality was predicted by the oxygenation index (OI) prior to or following CDH surgical repair.

*Methods:* The records of infants with a left sided CDH and without other congenital anomalies, who underwent surgical repair between April 2009 and March 2015, were examined. The oxygenation index was used to “quantify” the severity of lung function abnormality and reported as the best OI on day 1 after birth (OI<sub>BEST</sub>), the OI immediately prior to surgery (OI<sub>PRE</sub>) and at 1, 6, 12, and 24 hours post-surgery (OI<sub>1HR</sub>, OI<sub>6HR</sub>, OI<sub>12HR</sub>, OI<sub>24HR</sub>) respectively. The change in the OI index (delta OI), was calculated by subtracting OI<sub>PRE</sub> from post-operative OIs.

*Results:* The records of 37 CDH infants (median gestational age 35.8, range 31.5 – 41.4 weeks) were assessed; six died postoperatively. Neither the duration of anesthesia, the volume of crystalloids or colloids administered, nor the peak inflation pressures used during surgical repair were significantly correlated with postoperative mortality. Neither fetal tracheal occlusion nor use of a parietal patch significantly influenced mortality. The post-operative OI<sub>1HR</sub>, OI<sub>6HR</sub>, OI<sub>12HR</sub> showed weak evidence for a difference between survivors and non-survivors. An OI<sub>24HR</sub> of  $\geq 5.5$  predicted mortality with 100% sensitivity (95% CI, confidence intervals (CI) 40 – 100) and 93.1% specificity (95% CI, 77 - 99).

*Conclusion:* Neither the volume of intra-operative fluids administered nor the duration of anaesthesia was associated with post-operative death. The OI 24 hours post-surgery was the best predictor of an increased risk of mortality.

## **Key words:**

Anaesthetic duration; oxygenation index; crystalloids; colloids; survival predication; blood transfusion

## **Introduction**

Congenital diaphragmatic hernia (CDH) occurs in 1 in 2,500 to 5,000 live births but despite advances in prenatal diagnosis and neonatal intensive care, the mortality rates from CDH remain high between 10% and 23% in high and low-volume centers respectively (1-3). The greatest mortality is in the first 24 hours after birth, mainly due to severe lung hypoplasia. Current practice is to delay surgical correction of CDH beyond this period and repair is restricted to those who have achieved a measure of haemodynamic stability, but the ideal timing is unknown (4). Nevertheless, post-surgical mortality remains high, approximately 14% (5). Infants when undergoing CDH surgical repair require mechanical ventilation, anesthesia and frequently additional fluids and blood transfusion. Volume overload, transfusion related lung injury, baro-trauma, oxygen toxicity and the duration of anesthesia are factors known to adversely affect post-operative lung function in other populations (6-10). The oxygenation index (OI) is an assessment of lung function and has been used to predict outcome in CDH infants (11, 12). The aim of this study was to determine whether the intra-operative volume of intravenous (iv) fluids, the duration of anaesthesia or the perioperative OI were associated with post-operative death in infants with CDH. In addition, we wished to determine if the oxygenation index in the first 24 hours after birth or perioperatively predicted mortality. Our centre is a referral centre for fetuses with severe CDH to undergo fetal tracheal occlusion (FETO) with the aim of improving antenatal lung growth (13-15). We, therefore, also assessed whether post-operative mortality was higher in infants who had undergone FETO.

## **Methods**

The surgical, anesthetic and neonatal intensive care records of neonates with CDH who underwent surgical repair between March 2009 and April 2015 in a single surgical centre were reviewed. All infants were followed at least to hospital discharge. In order to standardize the study population and minimize confounding factors, neonates with a right sided CDH or who had any other major congenital anomalies were excluded from the analysis. This study included neonates with left sided CDH undergoing first surgical repair. The anaesthesia for CDH infants was always conducted by consultant paediatric anaesthetists. Infants during surgery and immediately before and after surgery were supported by conventional mechanical ventilation. Prior to surgery and in the immediate post-operative period infants received morphine and muscle relaxation.

The demographic data, antenatal treatment with FETO, oxygen requirement and ventilator pressures, arterial oxygen tensions in the first 24 hours after birth, immediately before surgery and during the 24 hours after surgery, the duration of anesthesia and volumes and types of colloid and crystalloids administered during surgery and the type of surgical repair were documented. Maintenance fluids (parenteral nutrition or 10% dextrose) were continued during anaesthesia. Fluid volumes entered into the analysis were the volumes given in addition to maintenance fluids.

The best oxygenation index (OI<sub>BEST</sub>) in the first 24 hours after birth and the OI immediately before surgery and 1, 6, 12, and 24 hours after surgery (OI<sub>PRE</sub>, OI<sub>1HR</sub>, OI<sub>6HR</sub>, OI<sub>12HR</sub>, OI<sub>24HR</sub> respectively) were calculated using the formula:

$$\text{Oxygenation Index} = \frac{\text{FiO}_2 \times \text{MAP}}{\text{PaO}_2}$$

FiO<sub>2</sub> (Fractional inspired oxygen concentration)

MAP (Mean airway pressure)

PaO<sub>2</sub> (Arterial partial pressure of oxygen)

In order to estimate the change in oxygenation postoperatively, the OI<sub>PRE</sub> was subtracted from post-operative OI<sub>1HR</sub>, OI<sub>6HR</sub>, OI<sub>12HR</sub>, and OI<sub>24HR</sub>. The resulting difference was delta (Δ) OI.

### *Statistics*

The student t test or Mann Whitney U test were used to explore differences in continuous variables depending on whether the data were normally distributed and the chi-squared test was used to compare proportions. All statistical analyses were performed with statistical software IBM-SPSS version 20 (IBM Corporation, New York, USA). Receiver operating characteristic (ROC) curve analysis was used and areas under the ROC curves calculated to determine whether factors which were significantly different on univariate analysis predicted mortality (16).

## Results

Forty-eight infants with left sided diaphragmatic hernia underwent surgical repair in the study period. Five infants with CDH were excluded from the study, all had right sided CDHS. The full complement of OI data and anaesthetic records were available for 37 infants. The demographics of those who did and did not have full datasets did not differ significantly (Table 1).

Six infants died at a median of 28 (range 5-273) days following surgery. The age at surgery was a median of five (range 2-18) days in the survivors group and seven (range 4-15) days in the non-survivors ( $p=0.14$ ). The median volume of fluids (mls/kg/hr) given to the non survivors did not differ significantly from that given to the survivors (colloids median 12.7 (range 0.00 – 56.75) versus median 18.17 (range 0.00 – 69.95) ( $p=0.4$ ) and crystalloids median 7.87 (range 2.81 – 37.34) versus median 21.23 (range 2.17 – 63.83) ( $p=0.1$ )). Three of the 31 survivors and three of the six non-survivors received a blood transfusion during surgery ( $p= 0.014$ ). No patient received platelets; FFP was given to one non-survivor and to five survivors and added no mortality risk (RR 1.03,  $p =0.9$ , 95% CI). Three non-survivors received succinylated gelatin compared to 26 of the survivors ( $p = 0.07$ ). The median duration of anaesthesia was 3.18 (range 1.41 – 7.71) hours for survivors and 4.88 (range 2.41 – 7.93) hours for non-survivors respectively and was not significantly different ( $p= 0.1$ ). The type of patch repair significantly influenced the duration of anaesthesia, but neither the  $OI_{24HR}$  nor the post operative mortality risk (Table 2). There were no significant differences between survivors and non survivors in the use of muscle relaxant ( $p=0.16$ ), sevoflurane ( $p=0.16$ ), isoflurane ( $p=0.2$ ), desflurane ( $p=0.5$ ), fentanyl ( $p=0.7$ ) or morphine ( $p=0.06$ ) during surgery.

FETO infants were born approximately four weeks earlier than the non-FETO infants, but there were no significant differences in the OIs of the FETO group compared to the non-FETO group.

Furthermore, FETO treated babies did not have a higher mortality than non- FETO treated babies following surgery (Table 3).

Although the  $OI_{1HR}$  and  $OI_{6HR}$  showed weak evidence for a difference between the non survivors and the survivors, the difference in the  $OI_{24HR}$  was statistically significant (Table 4, Figure 1). An  $OI_{24HR}$  of  $\geq$

5.5 predicted mortality with 100% sensitivity (95% CI, 39.76 – 100.0) and 93.1% specificity (95% CI, 77.23 - 99.15). An  $OI_{24HR}$  of  $\geq 5.5$  had a 14.5 fold relative risk of death (95% CI, 3.8 – 55.2,  $P=0.0001$ ). Neither the volume of colloid [median 15.78, range 0.0 - 69.9] (mls/kg/hour), the volume of crystalloid [median 18.01, range 2.1 – 63.8] (mls/kg/hour) nor the duration of anaesthesia (median 3.38, range 1.41 – 7.93 hours) correlated with  $\Delta OI_{24HR}$ .

## Discussion

We have demonstrated that neither the volume of fluids given nor the duration of anaesthesia was significantly associated with post-operative mortality. In addition, neither the volume of colloid or crystalloid nor the duration of anaesthesia correlated with the change in  $OI$  post-operatively, further suggesting certain “anaesthetic” factors did not significantly influence survival. Furthermore, infants who required a parietal patch had a significantly longer duration of anaesthesia, but this did not influence the oxygenation indices. Significantly more of the non survivors, however, received a blood transfusion and transfusion related lung injury has been shown in other populations to adversely affect post-operative lung function (6, 9). Importantly, we have demonstrated that  $OI_{24HR}$  had a high sensitivity and specificity in predicting post-operative mortality.

Approximately 50% of our study cohort were infants who had been antenatally diagnosed with a risk of severe pulmonary hypoplasia as indicated by their undergoing FETO. There was no significant difference in postoperative mortality between “FETO” and “non FETO” infants which may reflect that those who do not respond to FETO die before surgery (17). The FETO babies were born on average four weeks more prematurely than the non FETO group. Their oxygenation indices, however, at birth, before surgery and also 24 hours after surgery were not significantly different. This perhaps implies that FETO may improve outcomes in infants predicted antenatally with a poor outcome. We cannot, however, comment that the FETO infants might have died if they were not so treated. There is, however, an ongoing randomised trial, the TOTAL trial which is addressing that question (18).

$OI_{BEST}$  has been shown to be a significant predictor of death overall in CDH patients (12, 19, 20). The population we studied, however, had survived the initial stabilization period and were considered



suitable to undergo surgery on the basis of their physiologic status (21). This may explain why neither the OI<sub>BEST</sub> nor OI<sub>PRE</sub> was predictive of death.

This study has strengths and some limitations. Data were from contemporaneously collected data inputted into a neonatal database, surgical and anaesthetic records. Those with and without complete data did not differ significantly with regard to their demographics. To our knowledge, this is the first study which has assessed the relationship of the peri-operative oxygenation indices, the fluid volume and duration of anaesthesia to the postoperative mortality in CDH infants. We report a convenience sample size but, nevertheless, demonstrate significant differences in factors associated with post-operative mortality.

## **Conclusions**

The OI 24 hours post-surgery was significantly associated with an increased post-operative mortality risk. There was also a widening trend to differences in the OI between survivors and non-survivors in the 24 hours post surgery (Figure). These data suggest consideration should be given to escalation of therapy in the immediate post-operative period in infants with worsening OIs. FETO did not impose any additional risk upon post operative mortality or lung function.

## **Disclosures**

### *Ethical approval*

The local Ethical Committee classified this as a service evaluation project and that informed consent was not required.

### *Source of funding*

This study was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

### *Conflicts of interest*

No conflicts of interest declared.

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**Table 1: Demographics of those infants who were or were not included in the study**

**Data are demonstrated as median (range) or n**

	Studied	Excluded	P value
N	37	11	
Gestational age at birth (weeks)	35.9 (31.6 -41.4)	38.1 (34.1 – 39.9)	0.73
Birth weight in (kg)	2.66 (1.35 – 3.62)	2.58 (1.63 – 3.97)	1.0
Age at surgery (days)	4 (2-15)	3 (1-6)	0.42
FETO procedure	20	4	0.3
Died	6	1	0.5

**Table 2: Outcomes according to type of repair**

**Data are demonstrated as median (range) or n**

	Patch repair	Primary repair	P value
N	25	12	
Died	5	1	0.36
OI <sub>BEST</sub>	2.83 (1.2 – 12.10)	2.88 (1.77 – 5.80)	0.58
OI <sub>PRE</sub>	3.15 (1.6 – 5.6)	2.15 (0.9 – 4.0)	0.07
OI <sub>24HR</sub>	3.45 (1.4 – 32.6)	2.4 (1.0 – 5.6)	0.09
Crystalloids given ml/kg/hr	14.25 (2.17 – 62.37)	31.25 (5.09-63.83)	0.23
Colloids given ml/kg/hr	14.71 (0.00 – 56.75)	21.05 (0.0 – 69.95)	0.52
Duration of anaesthesia (hours)	4.46 (1.98 – 7.93)	2.86 (1.41 – 4.75)	0.002

**Table 3: Demographics and results according to FETO treatment**

**Data are demonstrated as median (range) or n**

	FETO	Non-FETO	P
n	20	17	
Died	5	1	0.1
Gestational age (weeks)	34.7 (31.6-41.0)	38.9(33.4-41.4)	< 0.001
Age at surgery (days)	4.5 (2-15)	4.0 (2.0 – 13)	0.4
OI <sub>BEST</sub>	2.89 (1.20 – 12.10)	2.82 (1.77 – 5.80)	0.4
OI <sub>PRE</sub>	3.00 (1.60 – 5.60)	2.65 (0.90 – 4.00)	0.7
OI <sub>24HR</sub>	3.7 (1.4 – 32.6)	3.0 (1.0 – 5.6)	0.2

**Table 4: The oxygenation index at birth and perioperative period**

**Data are demonstrated as median (range)**

	Survived	Died post-surgery	P value
N	31	6	
OI <sub>BEST</sub>	2.85 (1.60-06.61)	1.70 (1.20-12.10)	0.4
OI <sub>PRE</sub>	2.60 (0.90-05.60)	4.05 (1.6-05.00)	0.5
OI <sub>1HR</sub>	3.40 (1.20-27.60)	7.95 (3.20-26.00)	0.07
OI <sub>6HR</sub>	3.05(1.20-06.60)	6.40 (2.70 – 32.00)	0.08
OI <sub>12HR</sub>	3.50 (1.60-18.00)	11.05 (3.10 – 43.60)	0.08
OI <sub>24HR</sub>	3.00 (1.00-07.90)	8.10 (5.5 – 32.60)	<0.001



## FIGURE LEGEND

**Figure 1:** Box and Whisker plot of the oxygenation indices and on day one after birth (BEST), immediately prior to surgery (PRE-OP) during the immediate 24 hours following surgery (1 HR, 6 HR, 12 HR, 24 HR)

X represents outliers